MEG study of early cortical plasticity following multiple digit frequency discrimination training in humans

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1 Introduction

Animal studies have provided direct evidence for constant modification of cortical maps of an adult modulated by training [1, 2]. This representational remodeling was further studied by Wang et al. [3] showing that temporal coincident multiple digit stimuli resulted in integrated multiple receptive fields (fusion). Recent advances in human brain imaging techniques have made it possible to study cortical plasticity during learning using human subjects. Three recent MEG studies have reported plasticity changes after somatosensory stimulation. The first MEG study [4] used the protocol of Wang et al. and showed that extensive training produced a reversible decrease in the strength of equivalent current dipoles after perceptual learning, although fusion was predicted. The second MEG study [5] showed that passive tactile finger co-activation for 40 min reduced the Euclidean distance between median and ulnar nerve somatosensory evoked filed. The third MEG study [6] reported that sequences of tactile stimulation affect the organization of the primary somatosensory cortex after a brief training series. In this work, we used MEG to study early plasticity following multiple digit frequency discrimination training. Human subjects were trained to discriminate small changes in the frequency from a 21 Hz comparison steady-state stimulus applied for 1 s simultaneously to the fingertips of digits 2+3+4 of the right hand. After long training, synapses of fingertips (digits 2+3+4) receiving training would be strengthened by the simultaneous firing of their inputs through a process of Hebbian learning: stimulating digit 3 after the training would elicit a response from neurons of digits 2 and 4. Synaptic modifications are however unlikely immediately after short training, yet within a few trials subjective and behavioral measures show that a change has already taken place. This study produces evidence for changes over widely distributed brain areas as a concomitant of this early cortical plasticity.

2 Methods

Four healthy right-handed male subjects (N1-4, 39 ± 13.2 years) volunteered for the MEG experiment. One of the subjects (N2) repeated the same experiment 9 months later. For each subject, a plaster hand mold free of magnetic artifact was made to achieve stereotyped hand position and same skin site stimulated (Fig. 1). An elastic strip was also used to maintain contact of the fingers to the hand mold. A pair of electrodes was placed on each digit to generate the electrical stimulation, with a distance of 2.5 cm for digits 2 and 4, 3 cm for digit 3 and 2 cm for digit 5. The electrodes were located at the distal and middle segments (phalanges) of digits 2-5. Subjects experienced buzzing sensation at the distal segment. A Grass stimulator (model S8800) controlled the electrical current (0.2 ms duration at 2.0 to 3.0 mA). Stimuli were of 1 s duration and were separated by an interstimulus interval of 1s.

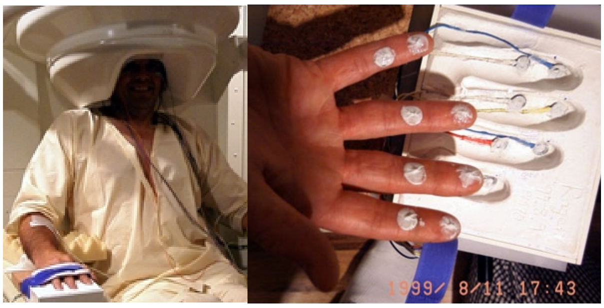

Figure 1: *Experiment setup and devices.*

Prior to the experiment, psychophysical calibration of the 21 Hz stimulus was performed for each subject on digits 2-5, in order to achieve a detectable and reliable, not too vigorous and comparable sensation across all digits. The level of stimulation for each digit was then fixed at this intensity level throughout the experiment, individually for each subject. After stimulus calibration, the procedures were administered in the following order. 1) Map I, the 21 Hz stimulation was applied separately to digits 3 and 5, 2 and 4, 2 and 3, 3 and 4, 3 and 5 in an intermixed order in 5 different runs. Sixty trials were delivered to each digit in the 2 runs of 3+5 and 30 trials in the other 3 runs. 2) Training (Fig. 2).

Subjects were trained to distinguish and estimate the frequency of a “comparison” stimulus S2 after a “standard” stimulus (S1) presented to digits 2+3+4. S1 was always 21 Hz, while S2 was either 21 Hz (50%) or varied from 22 to 29 Hz in steps of 1 Hz. As soon as S2 was over, subjects reported verbally the estimate of S2 and the confidence level of the guess. 2.5 s after S2 a visual feedback (0.3 s, the actual frequency of S2 in Arabic numerals) displayed on a screen 70 cm in front of subjects. 1.5 s later another pair of S1-S2 appeared. There were 3 training blocks and 192 pairs of S1-S2 in each block. The total training process took 3-4 h and the MEG signal was recorded for 1/3 of the training. 3) Map II, repetition of Map I after the training.

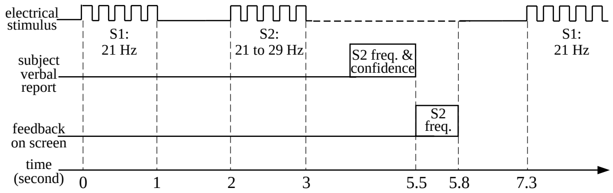

Figure 2: *Paradigm for the training blocks.*

We used the CTF whole head system (151 channels) to record the MEG signal and EEG electrodes to monitor artifacts from eye blinks (EOG), heart beats (ECG) and subject movements (EMG). The MEG signal was recorded continuously for each run, from DC to 150 Hz at a sample rate of 625 Hz. The environmental noise (e.g. power line) was first removed from the MEG signal and the data were then band-pass filtered in 1.25-150 Hz using the CTF software. Subject artifacts were removed using the independent component analysis (ICA) [7], as shown in Fig. 3. In this paper, we will discuss results from Map I/II data. The ICA-cleaned MEG signal was separated into trials of -500 to 1500 ms relative to the stimulus onset. Average for each digit was constructed separately in each of the 5 runs. Magnetic field tomography (MFT) [8] was applied to the averaged data to compute the 3D distribution of activity throughout the brain at each timeslice independently. The resulting brain images were superimposed on each subject’s MRIs. Objective statistical measure Kolmogorov-Smirnov (KS) test was used to identify brain areas that showed significant changes between the post- and pre-stimulus period by calculating the *p* values at 4913 voxels at each timeslice and selecting the areas with $p<0.005$. Cluster analysis was further applied to separate these areas into sub-areas with similar current flow direction. Regions of interest (ROI) were defined from these sub-areas as spherical regions with radius of 0.7-1.7 cm and labeled based on their anatomical locations. Activation curves for the modulus of the current density and along the main direction in these ROIs were calculated as a function of time.

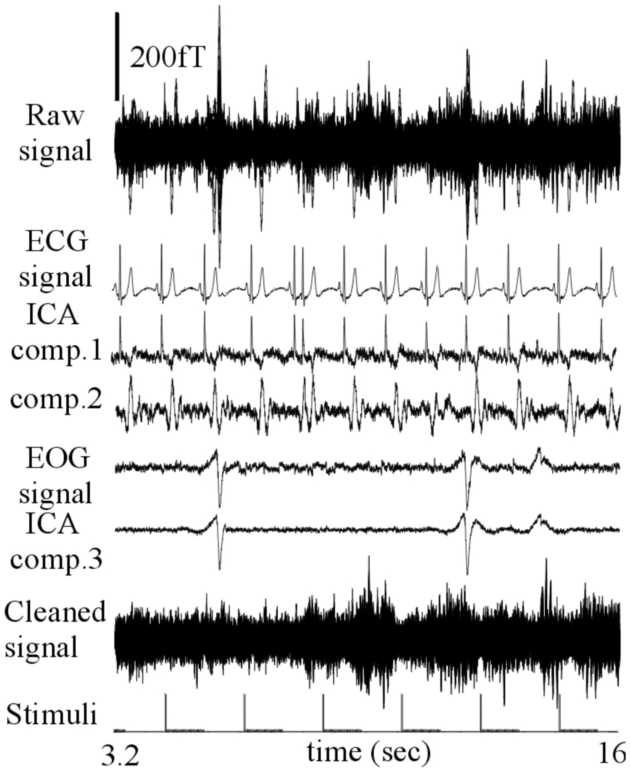

Figure 3: *ICA removed effectively the subject artifacts from the raw recorded MEG signal.*

3 Results

3.1 Behavioral results

Behavioral performance was evaluated at each comparison frequency greater than 21 Hz for each subject. Following Recanzone et al. [9], a performance score **P** was calculated by **P** = P(H) · [1 – P(FA)], where P(H) and P(FA) were the probability of a “hit” and a “false alarm”, respectively.

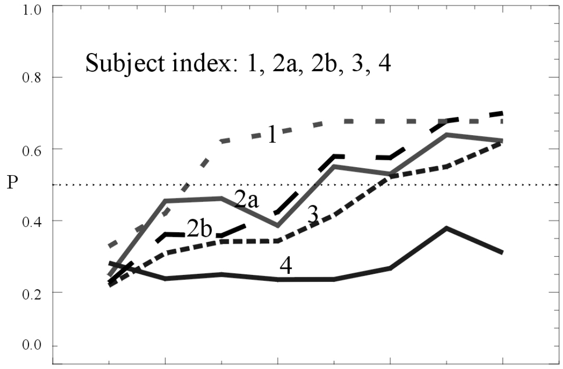

Figure 4: ***P** values for the 4 subjects with one subject (2a) repeating the experiment 9 months later (2b).*

Figure 4 shows the **P** values for each subject averaged over the 3 training blocks. The threshold to detect a frequency difference relative to 21 Hz when **P**=0.5 was about 5 Hz averaged across subjects. Subject N2 improved his performance slightly at the 2nd time of the experiment.

3.2 MEG results

The MFT analysis revealed strong activations in many areas around SI. Table 1 lists the ROIs we defined functionally for all the four subjects. In order to compare results across subjects, the ROIs for each subject were transformed into Talairach coordinates and then back-transformed into the MRI coordinates of subject N1 so that ROIs defined individually could be displayed on one common MRI background, as shown in Fig. 5.

hemi BA region Subj.	L 3 GPoC	L 3/2 GPoC	L 40 LPi	L 4 GPrC	R 3 GPoC	R 3/2 GPoC	R 4 GPrC	R 40 LPi	MP 7 PCu
N1		X	X			X	X		X
N2		X	X	X	X	X	X	X	X
N3	X		X	X	X	X		X	X
N4	X		X	X	X		X		X

Table 1: *ROIs for the four subjects. L, R and MP denote left, right and mid parietal. BA: Broadmann area; LPi: Lobulus parietalis inferior; GPoC: Gyrus postcentralis; GPrC: Gyrus precentralis; PCu: Precuneus. The activated area observed in respective subject is marked by* X.

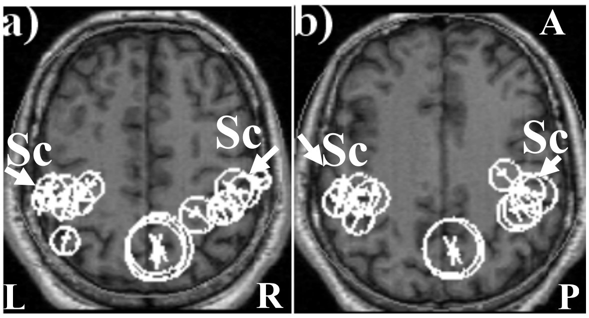

Figure 5: *ROIs (circles) for all four subjects transformed and superimposed onto two axial MRI slices of subject N1. The MRI slice in a) is about 1 cm superior to that in b). Big white arrows highlight the central sulcus (Sc).*

Figure 5 shows that clusters of activation across all four subjects. Activations in the left LPi and PCu areas were consistently identified, with identical locations and current density directions at the times of maximal activity for both maps. The most striking feature for the trained digit 3 was the increased coherence between the left LPi and PCu activations around the offset time of stimulation in Map II compared to Map I, as shown in Fig. 6. This increased coherence was evaluated by the paired t-test which yielded $p< 0.01$ (one tail). The increased coherence was also observed between areas of PCu and left SI (BA3/2 for subjects N1 and N2, BA3 for subjects N2 and N4, BA4 for N2 and N3). For the other three digits 2, 4 and 5, the coherence between left LPi and PCu areas changed in a less systematic way across runs and subjects (e.g. the paired t-test produced $p< 0.38$, 0.45 and 0.44 respectively for digit 2, 4 and 5). Following training the mean activations in the LPi area were reduced for all four subjects, and were also reduced in the PCu area for two subjects (N1, N2) (see Fig. 6). The decrease seemed to be more significant in the area around the left SI than in the mid-parietal area.

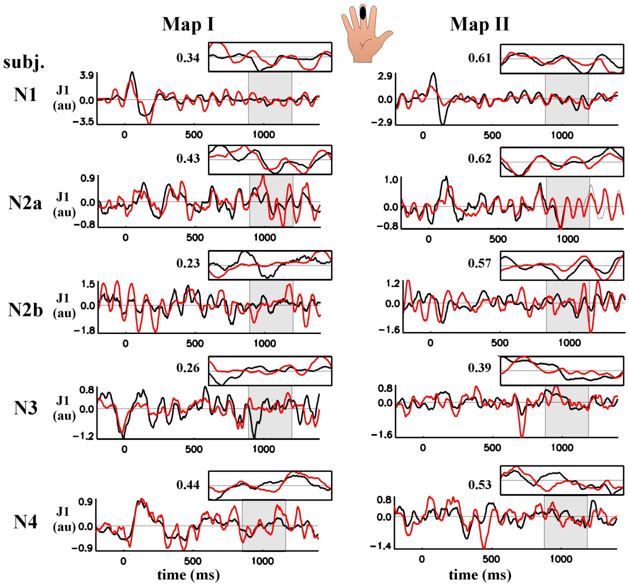

Figure 6: *Activation curves along the main direction of current density for the two ROIs in the LPi (dark curves) and PCu (light curves) areas for all four subjects when digit 3 was stimulated in the 1st mapping run of digits 3 and 5. Similar results were observed for the other run of 3+5. Activation at each timeslice was integrated over 50 ms. Map I and II are shown respectively on the left and right columns. The offset period (-900 to 1200 ms) is highlighted by gray squares, with inserts showing how similar the two curves look like (cross correlation coefficients are shown before the inserts). Note normalization was done across the two ROIs, but separately for the two maps and each subject. The curves in the inserts were normalized to their own maxima within the offset period.*

4 Discussion

There are several procedural differences between our study and other recent MEG studies on short-term plasticity [4-6]. First, we used the steady state instead of transient stimulation. We trained subjects with 21 Hz electrical stimulation that is within the resonant frequency of the human somatosensory system [10]. Second, we used the same stimulus for both mapping and training. Third, we examined changes over a shorter time period (three sessions of 1 hr each). We observed changes in many areas but in only a few consistently across subjects. In particular, we observed a mid-parietal activation in each subject that became more closely phase-coupled with activity around the contralateral SI toward the end of the stimulus. Ioannides et al. have recently identified a residual of 10 Hz oscillatory background activity (ROBA) in the auditory cortex [11]. ROBA was most pronounced in subjects who had extensive experience on the task; once a new protocol was introduced, ROBA was reduced or abolished, and only returned when the experiment was repeated within the same day or over a few of days. The increased coherence we observed between areas around contralateral SI and mid-parietal at the end of training was also most prominent around 10 Hz. The two may be signatures of early plasticity reflecting a dispersion of task-related brain activity in the spatial and temporal domains.

Acknowledgements

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